

# Control of Insecticide Exposure in Employment

## A Guide to Physicians for Dealing with Organic Phosphates

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PHYSICIANS in the rural areas of California are being called upon with increasing frequency to use their medical skills in the prevention of occupational disease as well as in its treatment. Today's technologic advances have placed within agriculture and allied industries an ever-increasing variety of valuable new chemicals, some of which present a formidable hazard when adequate safeguards are not employed.

Organic phosphate (phosphate ester) insecticides, with malathion a notable exception, are among the most hazardous materials yet used as pesticides. Parathion, TEPP (tetraethyl pyrophosphate), and Systox (demeton) are the highly toxic phosphate ester chemicals most widely used in California. It is in dealing with this group of insecticides that preventive medical services for employees are particularly valuable. The knowledge and experience gained by the physician who provides these services can be of considerable value to him in his practice. Phosphate and other insecticide problems are not confined to employees, although as a group they are subject to the most exposure. The careless handling of organic phosphate insecticides cost the lives of four children in California in 1954.<sup>8</sup>

The demand for the services of physicians to provide medical supervision for employed groups working with these insecticides is expected to increase. Not only are employers becoming more aware of the value of these programs, but the amounts of phosphate insecticides used in California are increasing rapidly.

In order to assist physicians who may be called upon to provide these services, there follows a short summary of information on organic phosphate poisoning, diagnosis and treatment, and an outline of the type of services which have been found to be of value in providing medical supervision for employees working with these materials.

Organic phosphate insecticides are esters of phosphoric acid and its derivatives. The only significant physiologic action they have is ability to inhibit or destroy the enzyme acetylcholinesterase. The signs and symptoms of poisoning are primarily the result of the intense stimulation which occurs when cholin-

• Increasingly larger amounts of the highly efficient and highly toxic organic phosphate insecticides, particularly parathion, tetraethyl pyrophosphate, and Systox (demeton), are being applied on California's farms. These insecticides have become an economic necessity to agriculture. They can be used safely when rigid precautions are utilized and when medical supervision is provided for employees regularly working with these chemicals.

The demand for the services of physicians prepared to supply this kind of industrial medical supervision is expected to increase in California.

The basic procedures through which effective medical supervision can be provided are outlined.

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esterase is insufficient to destroy acetylcholine accumulating in parasympathetic postganglionic fibers, in sympathetic ganglia, in the central nervous system and in myoneural junctions of striated muscle. The symptoms of parasympathetic stimulation (muscarinic effect) are most easily recognized and usually appear first.

These chemicals can be rapidly absorbed by any route, of which the skin is perhaps the most important. Organic phosphates are not skin irritants, so that usually no discomfort is noted while absorption is occurring. Inhalation of dusts and sprays can be hazardous. Contrary to popular belief, the phosphate ester insecticides either have a low degree of volatility or are so readily hydrolyzed that usually it is not the vapor given off which presents a problem. (The phosphate ester "nerve gases" are, however, highly volatile and have the same biological action as the phosphate insecticides.) On the basis of animal experimentation the minimum acute lethal oral dose of parathion and Systox (demeton) for man has been estimated at 12 to 20 mg.<sup>6</sup> Animal experiments indicate that TEPP may be somewhat more toxic than parathion.

Poisoning from these chemicals is an acute episode in which the patient is either dead or on the way to recovery in 24 to 48 hours. Sequelae are not expected. Chronic poisoning does not occur in the usual sense, although the effects of repeated smaller exposures to organic phosphates are cumulative when cholinesterase is destroyed faster than it can be regenerated. In these circumstances, the

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steadily declining level of cholinesterase activity produces no symptoms until the critical level is reached. Symptoms may then be noted suddenly after a small exposure.

Weakness, fatigue, giddiness, nausea and headache are usually among the first symptoms. The following train of symptoms and signs may be noted soon afterward (or they may be delayed): Abdominal cramps, blurred vision, miosis, lacrimation, profuse sweating, salivation, a feeling of constriction in the chest, difficult breathing, vomiting and diarrhea. In more severe poisoning, incoordination, mental confusion, oronasal frothing, drowsiness, fasciculations of voluntary muscles, loss of sphincter control, pulmonary edema, cyanosis, collapse, coma, convulsive seizures, respiratory failure and death can follow.

The most significant physical signs are a fixed miosis, excessive secretions and respiratory difficulty. The temperature is usually normal, the pulse is rapid and the blood pressure may be elevated. Increased bronchial secretions and bronchospasm will be evident upon examination of the chest.

The onset of symptoms of poisoning may be delayed, but is not to be expected more than 12 hours following exposure.<sup>4</sup> TEPP acts more rapidly than the other organic phosphate insecticides, and symptoms often appear shortly after significant exposure. A delay of several hours is more likely to occur after exposure to parathion or Systox.

#### DIAGNOSIS

Diagnosis is not difficult when the signs and symptoms just enumerated develop after exposure to a phosphate pesticide. Even when information concerning the patient's recent activities is not available, fixed miosis, greatly increased secretions, and respiratory difficulty in an acutely ill person are highly suggestive.

It is in the early stages or in milder cases of poisoning that the diagnosis may be more difficult. Conditions that have been confused with early or milder organic phosphate poisoning are: Heat stroke, asthma, respiratory infection and acute gastroenteritis. Several workers with acute poisoning have been hospitalized with tentative diagnosis of poliomyelitis. Poisoning from pilocarpine, from other parasympathomimetic drugs, and from the mushroom *Amanita muscaria* causes symptoms similar to those brought about by the phosphate anticholinesterase insecticides. (Fortunately, similar treatment is appropriate.)

It cannot be assumed that, just because a person works with organic phosphates, any illness which occurs is due to these chemicals; but it is always

advisable to hold such a patient under close observation until poisoning can be ruled out.

It is important to distinguish between poisoning from organic phosphates and that from other toxic pesticides. There is a variety of potentially hazardous agricultural chemicals unrelated to the organic phosphate group and unrelated to each other in terms of toxicology and treatment of poisoning.

The label on the original container provides the most accurate information about the pesticide to which a person may have been exposed. Regardless of the many trade names under which pesticides may be marketed, their labels must state the chemical or common name of the active ingredient. The following are common and chemical names of the highly toxic organic phosphate pesticides used to any extent at present in California:

Parathion (diethyl p-nitrophenyl thionophosphate)

Methyl parathion (metacide) (dimethyl p-nitrophenyl thionophosphate)

TEPP (tetraethyl pyrophosphate)

Systox (demeton) (diethoxy thiophosphoric acid ester of 2-ethyl mercaptoethanol)

OMPA (octamethyl pyrophosphoramidate)

EPN (ethyl p-nitrophenyl thionobenzene phosphonate)

(Malathion, chlorthion and dipterix are examples of newly developed organic phosphates of a much lesser degree of toxicity than those listed above. Trithion is a new phosphate pesticide of a moderate degree of toxicity. Thimet and phosdrin of high toxicity have also been recently introduced.)

The toxic organic phosphates are not marketed for household or garden use. A permit to purchase and apply them must be obtained from the County Agricultural Commissioner. His office may be able to provide information regarding the identity of a pesticide to which a patient may have been exposed.

Plasma and red cell cholinesterase activity determinations should be done for anyone in whom symptoms from exposure to organic phosphates are suspected. These tests are not only useful in confirming a diagnosis, but are necessary in order to advise a patient who works with these materials. Until cholinesterase has regenerated, he is particularly vulnerable to further exposure. The physician usually cannot wait for the result of the test before beginning treatment, however.

#### TREATMENT

Acute poisoning from phosphate ester pesticides is an extreme medical emergency. Lethal doses of these chemicals can be counteracted when treatment is applied early and vigorously.<sup>1</sup> Atropine is the physiological antidote. It acts by blocking the action of excessive acetylcholine. The dose, route and interval between injections is determined by what is necessary to keep the patient mildly atropinized for

the duration of symptoms. Repeated doses of atropine, much larger than the usual therapeutic amount, are required in acute poisoning and the intravenous route is recommended. For severe symptoms in adults, an initial dose of as much as 4 to 6 mg. of atropine sulfate is indicated. Maintenance doses of 2 mg. may be necessary at hourly or shorter intervals. For moderate symptoms an initial dose of 2 mg. is recommended, with lesser maintenance doses as required.<sup>3</sup> Favorable response to one or more injections of atropine does not guarantee recovery. Treatment must be continued throughout the emergency. However, the need for atropine after 48 hours is not usually expected. Contraindicated are theophylline, aminophylline, chlorotheophylline and morphine.<sup>6</sup>

When a severely poisoned patient is cyanotic, artificial respiration, preferably by mechanical means, should be started first and atropine given as soon as cyanosis is overcome.<sup>6</sup>

The patient should be decontaminated quickly by removal of clothing and bathing with soap and water to which soda or mild alkali has been added if available. The person carrying this out should wear gloves and the contaminated clothing should not be handled or shaken out. Gastric lavage is indicated if there is any indication that the insecticide has been ingested. The patient must be observed constantly. Equipment for artificial respiration and oxygen administration should be at the bedside. The need for it may arise suddenly.

Excessive bronchial secretions should be removed by whatever methods are appropriate—postural drainage, aspiration with a catheter and syringe, endotracheal intubation or tracheotomy. Giving fluids intravenously is contraindicated while there is excessive fluid in the respiratory tract.

Continuous observation and appropriate amounts of atropine are also important for patients with milder symptoms. It is not possible to predict whether more serious symptoms will follow. It is not safe to administer atropine and permit the patient to go home. Persons with no symptoms but who may have had significant exposure should be examined and held where they can be observed.

The minimum lethal dose of atropine has been reported as about 10 to 20 mg. for children and 80 to 130 mg. for adults.<sup>3</sup> Rarely, sensitivity to smaller doses has been reported. There is a good margin of safety between the therapeutic dose for organic phosphate poisoning and the fatal dose.<sup>3</sup> Persons with this kind of poisoning have an increased tolerance for atropine.

Atropine can precipitate an incipient glaucoma. Therefore, if suspicious symptoms referable to the eyes develop following treatment for organic phos-

phate poisoning, the patient should be seen by an ophthalmologist.

Atropine has no significant effect on cholinesterase activity and does not affect the validity of laboratory tests. By blocking the action of acetylcholine, atropine can control most of the symptoms of poisoning. It is not a specific chemical antidote acting to free the cholinesterase chemically inactivated by the phosphate ester pesticide.

Reports of recent experimental work indicate that specific antidotes may soon be developed, but none are as yet ready for use in the treatment of human poisoning.

#### CHOLINESTERASE ACTIVITY DETERMINATION

There are several methods by which cholinesterase activity can be determined. The basis for most techniques is the direct or indirect measurement of the acetic acid liberated in a system where the cholinesterase in a known amount of red cells or plasma hydrolyzes acetylcholine, which has been added in excess. Cholinesterase hydrolyzes acetylcholine to acetic acid and choline. The amount of acetic acid liberated will depend upon the concentration of red cell or plasma cholinesterase.

The Michel electrometric method, particularly the modification which permits the use of fingertip blood, is the most widely used technique. This method provides a practical combination of simplicity with a reasonable degree of accuracy. A potentiometer is used to measure the lowering of pH produced by the liberated acetic acid. The results are reported in  $\Delta$  pH units per hour. Reliability of duplicate determinations of the same specimen should be within 15 per cent.<sup>5</sup>

The normal range for plasma is about 0.41 to 1.65  $\Delta$  pH units with an average of 0.91  $\Delta$  pH units. The normal range for red cells is 0.55 to 1.25  $\Delta$  pH units with an average of 0.86  $\Delta$  pH units.<sup>7</sup> A person with no exposure to anticholinesterase chemicals shows a fairly constant cholinesterase activity with somewhat more variation in plasma values than in red cell values. However, there may be wide disparity of cholinesterase activity between one unexposed person and another, which can be considered normal. Therefore, in the medical supervision of employed groups using phosphate insecticides, it is more accurate to base interpretation of each employee's periodic cholinesterase tests on his own normal values as determined before exposure to these chemicals.

On the basis of what is known about the reliability of the laboratory procedure and the variation in cholinesterase activity inherent in the individual,<sup>2,5,7</sup> an arbitrary estimate of significance can be made when red cell or plasma cholinesterase drops to less

than 75 per cent of the individual's pre-exposure value. When the pre-exposure or baseline value is not known, a decrease in red cell or plasma cholinesterase to 60 or 70 per cent of the average for the general population may be looked upon as suspicious. A fairly well established practical standard for determining when a person should be removed from exposure to phosphate ester pesticides is a decrease of either plasma or red cell cholinesterase activity to 50 per cent of "normal," based preferably on the individual's normal value. He should not return to exposure to organic phosphate pesticides until both plasma and red cell cholinesterase have increased to above 75 per cent of his normal. Phosphate poisoning can fairly well be ruled out if red cell cholinesterase is above 50 per cent of the individual's normal or if subsequent serial tests do not show that a decrease of this magnitude has occurred. Symptoms usually do not appear until red cell cholinesterase has dropped to between 25 and 50 per cent of normal. In fatal poisoning, pronounced cholinesterase inhibition (0 to 10 per cent of normal) is the only specific finding.<sup>4</sup>

Plasma cholinesterase is a nonspecific enzyme; that is, it hydrolyzes certain other esters of choline. It is a more sensitive indicator of absorption of organic phosphate chemicals and is reduced earlier than the specific cholinesterase in the red cells. Plasma cholinesterase activity bears no relationship to the cholinesterase of the nervous system, and is affected by certain other chemicals and conditions, notably reduced liver function. Red cell cholinesterase is specific for acetylcholine and bears a relationship to the nervous system enzyme. It is, therefore, an indicator of more serious inhibition and is related to actual signs and symptoms of poisoning. Plasma cholinesterase may be reduced to zero without symptoms, provided the red cell cholinesterase has not dropped to the critical level. However, it is more often the case that red cell cholinesterase also is considerably diminished when plasma values are low. Determining both plasma and red cell cholinesterase provides two kinds of information—one kind helpful in assessing exposure early, and the other in indicating extent of exposure.

In man, it takes about three weeks for plasma cholinesterase activity to recover from zero to normal. Red cell cholinesterase recovers more slowly. At present, there is no method known for speeding up the natural recovery process.

#### SUPERVISION OF EXPOSED PERSONS

The preventive medical services which a physician provides to a group of employees at the request of their employer are particularly valuable when the physician becomes well acquainted with the nature

and details of the work that the employees do. The fundamental purpose of this type of medical program is to provide a continuing check on the effectiveness of the protective equipment and work methods which are used to prevent exposure to phosphate pesticides.

Although medical supervision is always indicated where employees are regularly using hazardous materials, it has perhaps more to offer where there is exposure to organic phosphates. There are not many of the acutely toxic chemicals used in industry for which there is available both a laboratory test which can help detect excessive exposure before illness appears, and an effective antidote to combat poisoning should an accident occur in spite of all precautions. For employees working with these chemicals, the availability of adequate treatment of poisoning is greatly enhanced when there is a physician who knows the work situation and has made preparations to meet an emergency.

The cost of the medical program is a necessary expense of operation where hazardous materials are used in employment, and is, of course, assumed by the employer.

Although the needs and circumstances of employed groups differ and the approaches to providing medical supervision of them may vary, there are certain basic procedures: They are of two kinds: Procedures requiring particular attention when the program is initiated, and procedures that are carried out on a continuing basis.

*Initial Procedures:* It is desirable that each employee have a physical examination and that a complete medical and occupational history be taken. Workers who handle hazardous materials regularly should be in good physical condition. The initial examination provides the physician with an excellent opportunity for informing the employee of the nature of the hazard in his work.

Cholinesterase activity determinations for both plasma and red cells should be done on at least two different occasions to establish the normal level for each employee at a time when he has had no exposure to phosphate ester insecticides for three weeks, preferably longer. Where a local laboratory does not regularly perform these tests but is interested in doing so, it can obtain expert advice on the subject from the Industrial Hygiene Laboratory of the State Health Department. A list of laboratories in California known to be prepared to carry out these tests is available on request from the same source.

Prearrangements for managing acute poisoning should be made so that no time will be lost in administering first aid and medical treatment. The physician should carry an ample supply of injectable atropine in his emergency bag. Further, the physi-

cian can provide the employer with instructions on first aid. A copy of these instructions can be given to each employee and posted at the places of work. The physician can designate an alternate or a panel of physicians to be called when he cannot be reached. Because serious symptoms of poisoning may not develop until several hours after exposure, each employee should carry with him the name and phone numbers of the physicians in case he becomes ill while away from work.

Whether or not employees should carry atropine is a matter requiring considered medical judgment. The situation differs among employed groups, both with regard to the distance from medical care and the willingness of the workers to follow instructions. Two tablets of atropine (0.6 mg. each) can temporarily cover up early symptoms of poisoning and give a false sense of security. There may then be a delay in obtaining medical care and, in some instances, the employee may go back to more work with the insecticide. In acute poisoning, oral administration of atropine is of little assistance because of the attendant nausea and vomiting, and the need for larger doses parenterally.

In certain circumstances, letting the worker have atropine to keep on hand for use if needed may help the physician in the differential diagnosis between milder phosphate insecticide poisoning and other conditions. Employees can be instructed to take one or two atropine tablets when any symptoms develop which could be due to these insecticides, and to report to the physician at once. If the patient shows the effects normally expected of atropine, this fact is a point of evidence against poisoning. If, on the other hand, the usual effects of atropine are absent, this is evidence for phosphate insecticide poisoning.

Taking atropine as a prophylactic measure is not recommended.

*Continuing Procedures:* Cholinesterase activity determinations for plasma and red cells should be carried out periodically for employees while they are regularly exposed to organic phosphate insecticides. The optimum interval for these tests can best be determined by experience with the employed group in question. Intervals of one week or less may be appropriate when exposure is considerable. Where controls are operating well, or smaller amounts of insecticide are being handled, two or three week intervals may be adequate. The period between tests may be different among individuals within the same group of employees.

The cholinesterase activity determinations are of most value when they are carried out and the results reported to the physician within a day of the time the group of workers appears for the tests. It is desirable that the initial report include the method

used and that all reports give the numerical results and the per cent of the individual's baseline value that each result represents. The date and time the blood was drawn should also appear.

In general the interpretation is the same regardless of which of the phosphate ester chemicals or mixture of them is being used. Experienced physicians have worked out various methods of determining at what cut-off levels of cholinesterase activity employees should be removed from exposure or returned to work. However, until a physician gains experience he may be at a loss as to where to start. For this reason, the following scheme is suggested, although it may not prove to be the optimum for some groups:

*Satisfactory:* When both plasma and red cell cholinesterase activity are 75 per cent or more of the individual's baseline value.

*Caution—Showing significant exposure:* When either plasma or red cell cholinesterase activity drops to 50 to 74 per cent of the baseline value.

*Stop work with phosphate insecticides:* When either plasma or red cell cholinesterase activity drops to below 50 per cent.

*Back to usual work:* When both plasma and red cell cholinesterase activity have risen to 75 per cent or above the individual's baseline value.

A running graph kept for each employee, on which is plotted the results of the periodic cholinesterase tests is a useful device for visualizing trends. Other pertinent events can be included on the graph.

The report to the employer can include the above categories and the names of the employees falling in each, together with any recommendations about the working situation the physician feels are warranted.

When red cell cholinesterase values fall below 50 per cent, it is desirable for the laboratory to report by phone to the physician and for the physician to notify the employer and the employee as soon as possible. Further exposure is hazardous and the worker should be examined by the physician for signs and symptoms of poisoning. It is desirable for future reference to take the opportunity to discover at what level of cholinesterase inhibition the worker shows signs or symptoms. (Miosis and possibly wheezing may be either a local or a systemic effect. If only a local effect, the cholinesterase activity will not be significantly low.)

The workers should, of course, be instructed to report to the physician when any signs or symptoms appear which could be due to phosphate chemicals, or if there is any question of having received a significant exposure.

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